A multicentre, open-label, randomized comparative study of tigecycline versus ceftriaxone sodium plus metronidazole for the treatment of hospitalized subjects with complicated intra-abdominal infections

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Abstract

Tigecycline (TGC) has demonstrated clinical efficacy and safety, in comparison with imipenem/cilastatin in phase 3 clinical trials, for complicated intra-abdominal infection (cIAI). The present study comprised a multicentre, open-label, randomized study of TGC vs. ceftriaxone plus metronidazole (CTX/MET) for the treatment of patients with cIAI. Eligible subjects were randomized (1:1) to receive either an initial dose of TGC (100 mg) followed by 50 mg every 12 h or CTX (2 g once daily) plus MET (1–2 g daily), for 4–14 days. The primary endpoint was the clinical response in the clinically evaluable (CE) population at the test of cure (TOC) assessment. Of 473 randomized subjects, 376 were CE. Among these, clinical cure rates were 70.4% (133/189) with TGC vs. 74.3% (139/187) with CTX/MET (95% CI −13.1 to 5.1; p 0.009 for non-inferiority). Clinical cure rates for subjects with Acute Physiological and Chronic Health Evaluation II scores ≥10 were 56.8% (21/37) with TGC vs. 58.3% (21/36) with CTX/MET. The microbiologic response was similar between the two treatment arms, with microbiological eradication at TOC achieved in 68.1% (94/138) of TGC-treated subjects and 71.5% (98/137) of CTX/MET-treated subjects. (The most frequently reported adverse events (AEs) for both treatment arms were nausea (TGC, 38.6% vs CTX/MET, 27.7%) and vomiting (TGC, 23.3% vs CTX/MET, 17.7%). Overall discontinuation rates as a result of an AE were 8.9% and 4.8% in TGC- and comparator-treated subjects, respectively. The results obtaned in the present study demonstrate that TGC monotherapy is non-inferior to a combination regimen of CTX/MET with respect to treating subjects with cIAI.

Keywords: Antibiotic, complicated intra-abdominal infection, glycylcycline, metronidazole, monotherapy ceftriaxone, randomized trial, tigecycline

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Introduction

Tigecycline (TGC) is an expanded broad-spectrum antibiotic with *in vitro* activity against bacterial pathogens associated with intra-abdominal infections [1–4]. TGC has been demonstrated to be non-inferior to imipenem/cilastin in two previous phase 3 efficacy and safety trials for treatment of complicated intra-abdominal infection (cIAI) [5,6]. The present study was designed to compare the efficacy and safety of TGC with a commonly used combination of antibiotics, ceftriaxone sodium plus metronidazole (CTX/MET), for treatment of hospitalized patients with cIAI.

Materials and Methods

Design

The present trial was a phase 3b/4, multicentre, open-label, prospective, randomized, comparative trial of hospitalized adult subjects with a known or suspected diagnosis of cIAI. The study was conducted in 53 centres in the USA, Canada and Latin America. The two treatment arms of the study were intravenous (IV) TGC (initial 100 mg dose infused over a 30-min period, followed by 50 mg IV every 12 h) or IV CTX (2 g once daily) plus MET (1–2 g daily, given in divided doses).

The primary objective was to demonstrate the safety and noninferiority of the clinical efficacy of TGC vs. CTX/MET. The primary endpoint was the clinical response in the clinically evaluable (CE) population at the test of cure (TOC) assessment.

The secondary objectives were: (i) to compare the microbiological efficacy of TGC vs. that of CTX/MET and (ii) to evaluate *in vitro* susceptibility data on TGC for the range of bacteria that cause cIAI.

Institutional review board/ethics committee approval was obtained for each study site. Written informed consent was obtained from each subject or legal guardian prior to participation in the study. Eligible subjects were known or suspected to have a cIAI with fever and/or leucocytosis, leucopaenia, or left shift on cell differential count (>10% immature band forms). Subjects had to have undergone a laparotomy, laparoscopy or percutaneous drainage for an IAI within one calendar day prior to, or after, the first dose of study drug.

Subjects were excluded if they received more than1 day of antibiotic therapy prior to enrollment.

The study drug was administered for a minimum of 4 days and a maximum of 14 days. Subjects returned for TOC assessment 10–21 days after the last dose of study drug, and a clinical response of cure or failure, or an indeterminate response, was determined by the investigator. Clinical response was defined as: cure (the study drug and initial intervention resolved the IAI); failure [additional surgical or radiological intervention and/or additional antibiotic treatment were necessary to cure the infection, death after day 2 as a result of the infection or a treatment-related adverse event (AE) or discontinuation of study drug due to a treatment-related AE]; or indeterminate (lost to follow-up; death within 2 days of first dose of test compound or death after 2 days of test compound because of reasons unrelated to infection).

Randomization

Subjects were stratified at randomization to two groups on the basis of their Acute Physiological and Chronic Health Evaluation (APACHE) II score: ≤10 or >10. Each group was randomly assigned in a 1:1 ratio to receive either TGC or CTX/MET, according to a central computerized randomization/enrollment system generated by Wyeth Pharmaceuticals.

Bacterial isolates

Baseline aerobic and anaerobic cultures were obtained from the primary intra-abdominal site of infection during the qualifying surgical procedure. Two sets of blood culture were obtained prior to administration of the first dose of study drug. All recovered isolates were identified and tested at a central laboratory (Covance Central Laboratory Services, Inc., Indianapolis, IN, USA) by a standard procedure approved by the CLSI Subcommittee on Antimicrobial Susceptibility Testing. For TGC, Food and Drug Administration approved breakpoints were used.

Analysis populations

Several populations were defined for analysis. Subjects who provided written informed consent and were randomized were included in the intent-to-treat (ITT) population. Subjects who received at least one dose of study drug formed the modified intent-to-treat (mITT) or safety population. Subjects in the mITT population who met minimal disease criteria of a cIAI were included in the clinical modified intent-to-treat (c-mITT) population. From the c-mITT population, the primary efficacy population, the CE population was defined as subjects who met all inclusion and exclusion criteria, received therapy for at least 4 days in case of clinical cure or at least 2 days in case of clinical failure, received no potentially effective concomitant antibacterial therapy after the first dose of study drug through the TOC assessment, and had a TOC visit 8–44 days after the last dose of study drug. The microbiologically positive mITT population (m-mITT) met the minimal disease criteria and had a confirmed baseline isolate.

The microbiologically evaluable (ME) population was defined as subjects who were CE and also had a baseline isolate susceptible to both TGC and comparator.

Statistical analysis

Statistical analysis was performed by the Clinical Biostatistics Department Quintiles (Bloemfontein, South Africa). Assuming an eligibility rate of at least 70%, approximately 430 subjects were to be enrolled to obtain 301 clinically eligible subjects. Assuming that the two treatment groups were equally effective, with favourable clinical response rates (i.e. cure) of 80% at the TOC assessment, 151 subjects per treatment group were required to ensure with 90% probability (i.e. 90% power) that the lower limit of a two-sided 95% CI for the true difference (tigecycline minus the comparator) in efficacy was >−15%.

The primary end point was the clinical response at the TOC visit for the CE population. Primary analysis was applied to the CE population with a comparison of the clinical success rate (cure vs. failure) between treatment groups. Non-inferiority (NI) was concluded if the lower limit of the two-sided 95% confidence interval (corrected for continuity) was >−15. Supplementary analyses were performed for the mITT, c-mITT, m-mITT, ME, and CE populations. An interim analysis was not planned for the present study.

Analysis of safety data included a comparison of the proportions of subjects experiencing AEs, and potentially clini-

cally important laboratory and vital sign values. Chi-square or Fisher's exact test were used to compare proportions (e.g. efficacy response, AEs). Analysis of variance and Kaplan–Meier methods were employed to assess treatment group differences in length of hospital stay, time to defervescence and duration of IV antibiotic treatment.

Results

Subject disposition and analysis populations

Between September 2005 and February 2008, 473 subjects were enrolled in the study at 53 sites in six countries in North and South America. After elimination of six subjects from the study prior to receiving study drug (Fig. 1), 467 subjects constituted the mITT or safety population (TGC, *n* = 236; CTX/MET, *n* = 231), with 448 subjects exhibiting clinical evidence of a cIAI (c-mITT). Within this latter cohort, 376 subjects were CE (TGC, *n* = 189; CTX/MET, *n* = 187) and, from 321 subjects, a baseline isolate was recovered from an intra-abdominal or blood source, comprising the m-mITT population. A total of 275 subjects (TGC, *n* = 138; CTX/MET, *n* = 137) met clinical evaluability criteria and had a baseline isolate recovered from an intra-abdominal source or blood source that was susceptible to the study drugs (ME population). Forty-eight TGC and 49 CTX/MET subjects were excluded from the CE population; primary reasons were 'no clinical evaluation at the TOC assessment' (TGC, *n* = 15; CTX/MET, *n* = 10) and 'use of prohibited/concomitant antibiotics' (TGC, *n* = 11; CTX/MET, *n* = 12). Rates and reasons for exclusion were generally similar between treatment groups.

Demographic and baseline medical characteristics

Demographic characteristics of the mITT population were similar between the two treatment groups (Table S1). Most subjects were males (64.7%) and Caucasian (65.3%). The mean age was 48 years. There were no significant differences

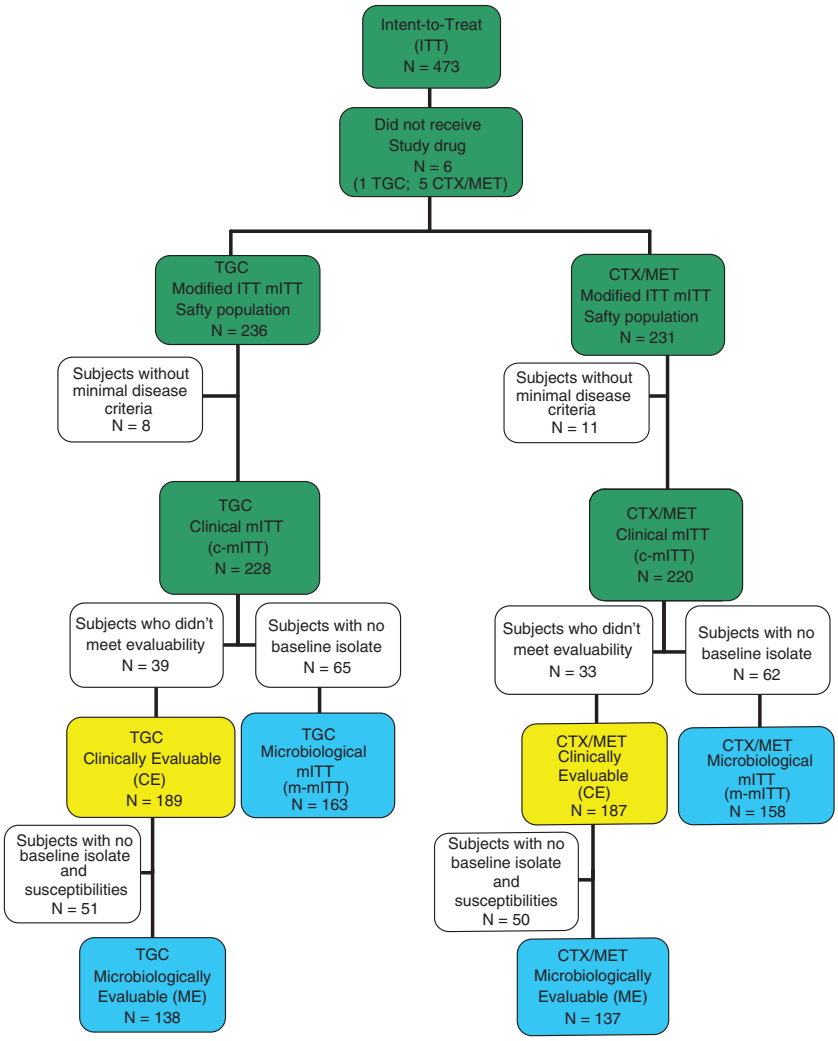

FIG. 1. Study flow diagram. c-mITT, Clinical modified intent-to-treat; CTX/MET, ceftriaxone plus metronidazole; ITT, intent-to-treat; mITT, modified intent-to-treat; TGC, tigecycline.

between the treatment groups in the number or types of baseline infections. The most common diagnosis was complicated appendicitis (52%), followed by complicated diverticulitis (12%), purulent peritonitis (11%) and intra-abdominal abscess (11%) (Table 1).

A proportion of subjects received at least 72 h of antibiotic therapy before enrollment and were enrolled in the study as prior antibiotic failures (10.6% TGC, 4.3% CTX/MET, p 0.010). A total of 335 (72%) subjects in the mITT population had peritonitis at the time of qualifying surgical procedure. Abscesses were present in 270 (59%) subjects: 49% of these subjects had a single abscess, whereas 10% had multiple abscesses. After completion of the qualifying surgical procedure or percutaneous drainage, 213 (90%) subjects in the TGC arm and 209 (91%) subjects in the CTX/MET arm had minimal or no residual contamination.

Clinical efficacy

In the CE population, clinical cure was reported for 133 of 189 (70%) of the TGC-treated subjects and 139 of 187 (74%) of the comparator arm (−4.0; 95% CI −13.1 to 5.1; p 0.009 for NI) (Table 1). Clinical cure rates for the ME population were 66% and 70% (−3.4; 95% CI −14.5 to 7.8; p 0.020 for NI), respectively (Tables 2 and 3). In the c-mITT population, clinical cure was reported for 145 of 228 (64%) of the TGC-treated subjects and 155 of 220 (71%) of CTX/MET-treated subjects (−7.0; 95% CI −15.8 to 1.08; p 0.038 for NI).

There were no significant differences in clinical response between treatment groups based on primary diagnosis or APACHE II score (Table 1). For complicated appendicitis, clinical cure at TOC was similar between TGC and CTX/MET [74% vs. 77%, respectively (−3.9; 95% CI −17.0 to 9.3)] and complicated diverticulitis [65% vs. 72%, respectively (−7.0; 95% CI −38.8 to 24.8)]. Subjects with intra-abdominal abscess(es) had lower cure rates [52% vs. 47%, respectively (5.0; 95% CI −31.0 to 41.0)]. Seventeen subjects in the ME population had concomitant bacteraemia. In this subpopulation, TGC was associated with clinical cure rates of seven of eight (88%) and CTX/MET with six of nine (67%) subjects, respectively. There were no significant differences between groups in terms of cure rates or eradication.

Microbiologic efficacy

Escherichia coli followed by members of the *Bacteroides fragilis* group were the most commonly isolated bacteria. For the ME population, clinical cure rates for the different pathogens were similar between the two treatment groups (Table 2). At TOC in the ME population, infections were cured in

TABLE 2. Clinical cure rates at test of cure by pathogen [microbiologically evaluable (ME) population]

	TGC ME, *n/N* (%)	CTX/Met ME, *n/N* (%)
Escherichia coli	67/96 (69.8)	61/92 (66.3)
Klebsiella spp.	6/15 (40.0)	13/19 (68.4)
Pseudomonas aeruginosa	14/20 (70.0)	7/12 (58.3)
Bacteroides fragilis group[a]	51/80 (63.8)	53/81 (65.4)
Clostridium spp.	16/19 (84.2)	10/12 (83.3)
Peptostreptococcus spp.	6/10 (60.0)	8/10 (80.0)
Enterococcus spp.	20/29 (69.0)	8/19 (42.1)
Staphylococcus aureus	2/3 (66.7)	2/3 (66.7)
Streptococcus anginosus	15/19 (78.9)	14/20 (70.0)

[a]*B. fragilis* group = *B. fragilis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Parabacteroides distasonis*.
TGC, Tigecycline; CTX/MET, ceftriaxone plus metronidazole.

TABLE 1. Cure rate at test of cure by primary diagnosis and Acute Physiological and Chronic Health Evaluation (APACHE) II score (clinically evaluable population)

Diagnosis	TGC, *n/N* (%)	CTX/MET, *n/N* (%)	Difference TGC – CTX/MET (95% CI)[b]
Complicated appendicitis	72/98 (73.5)	75/97 (77.3)	−3.9 (−17.0, 9.3)
Purulent peritonitis	17/23 (73.9)	16/18 (88.9)	−15.0 (−43.0, 13.1)
Intra-abdominal abscess[a]	11/21 (52.4)	9/19 (47.4)	5.0 (−31.0, 41.0)
Complicated diverticulitis	13/20 (65.0)	18/25 (72.0)	−7.0 (−38.8, 24.8)
Perforation of the intestine	9/14 (64.3)	13/17 (76.5)	−12.2 (−50.9, 26.5)
Gastric/duodenal perforation	8/9 (88.9)	7/7 (100.0)	−11.1 (−44.3, 22.1)
Complicated cholecystitis	3/4 (75.0)	1/4 (25.0)	50.0 (−35.0, 100.0)
Overall adjusted difference[c]			−6.3 (−15.3, 2.7)
APACHE II score			
<10	112/152 (73.7)	118/151 (78.1)	−4.5 (−14.7, 5.8)
10–15	17/30 (56.7)	16/28 (57.1)	−0.5 (−29.4, 28.5)
>15	4/7 (57.1)	5/8 (62.5)	−5.4 (−68.4, 57.7)
Overall[d]	133/189 (70.4)	139/187 (74.3)	−4.0 (−13.1, 5.1)[e]

[a]As defined by the investigator.
[b]Calculated using asymptotic method corrected for continuity.
[c]Adjusted difference and 95% CI calculated using a generalized linear model with binomial probability function and identity link.
[d]Estimates of the difference, CI and hypothesis tests are weighted by using minimum risk weights (method of Mehrotra and Railkar).
[e]Test for non-inferiority, p 0.009.
TGC, Tigecycline; CTX/MET, ceftriaxone plus metronidazole.

TABLE 3. MIC ranges and MIC_{50} and MIC_{90} values for selected primary baseline isolates (microbiologically evaluable population)

Baseline isolate (*n*)	Tigecycline (mg/L)				Ceftriaxone (mg/L)				Metronidazole (mg/L)			
	Minimum	Maximum	MIC_{50}	MIC_{90}	Minimum	Maximum	MIC_{50}	MIC_{90}	Minimum	Maximum	MIC_{50}	MIC_{90}
Bacteroides fragilis (53)	0.25	32.0	1.0	4.0	16.00	256.00	32.0	128.0	0.12	4.00	1.0	2.0
Clostridium perfringes (8)	0.12	4.00	NA	NA	0.06	4.00	NA	NA	0.50	16.00	NA	NA
Enterococcus faecalis (19)	0.03	0.25	0.06	0.12	8.00	64.00	64.0	64.0				
Escherichia coli (188)	0.06	1.00	0.12	0.25	0.03	16.00	0.06	0.12				
Klebsiella pneumoniae (29)	0.25	0.50	0.25	0.50	0.03	0.12	0.06	0.12				
Staphylococcus aureus (6)	0.06	0.25	NA	NA	2.00	64.00	NA	NA				
Streptococcus anginosus (39)	0.03	0.12	0.03	0.03	0.06	0.50	0.25	0.50				

NA, Not available for isolates from a population of <10 subjects.

68.0% and 67.0% of all monomicrobial and polymicrobial infections, respectively, in the TGC-treated subjects, and 71.5% and 68.3% of all monomicrobial and polymicrobial infections, respectively, in the CTX/MET-treated subjects. *In vitro* activity against selected baseline isolates is shown in Table 3.

Adverse events

Safety and tolerability of TGC, including the frequency and distribution of AEs, were similar to those of CTX/MET. One hundred subjects reported one or more serious adverse events (SAEs) during the study (TGC, *n* = 51; CTX/MET, *n* = 49). There were no statistically significant differences between treatment groups in the overall incidence of subjects reporting one or more SAEs (p 1.000) or in the incidences of any reported SAE term or body system. The most frequently reported SAEs overall were abscess (31/467; 6.6%), infection (7/467; 1.5%), respiratory failure (7/467; 1.5%), abdominal pain (6/467; 1.3%) and ileus (6/467; 1.3%).

Treatment emergent adverse events (TEAEs) in the TGC treatment arm (195/236; 82.6%) did not differ significantly from the CTX/MET treatment arm (189/231; 81.8%) (p 0.904) (Table 4). The most frequently reported TEAE in either treatment group was nausea, reported in 91 of 236 (38.6%) TGC-treated subjects and 64 of 231 (27.7%) CTX/MET-treated subjects. Vomiting was the second most frequently reported TEAE, reported in 55 of 236 (23.3%) TGC-treated subjects and 41 of 231 (17.7%) CTX/MET-treated subjects. Significantly more subjects treated with TGC reported (or were diagnosed with) the TEAEs of nausea, oral moniliasis, leukocytosis and deep venous thrombosis. Significantly more subjects treated with CTX/MET reported the TEAEs of generalized oedema, atelectasis and taste perversion. Of the 26 subjects reporting AEs of infection, *Clostridum difficile* was reported in only one CTX/MET subject.

Twenty-one of 236 (8.9%) TGC-treated and 11 of 231 (4.8%) CTX/MET-treated subjects discontinued study drug because of an AE (p 0.099). There were no significant differences between treatment groups in frequency of any single AE leading to the discontinuation of study drug. The most frequently reported AE leading to discontinuation of study drug were nausea in seven of 467 subjects (1.5%) and abscess in seven of 467 subjects (1.5%).

TABLE 4. Treatment-emergent adverse events[a] profile (modified intent-to-treat)

Adverse event	TGC, *N* = 236, *n* (%)	CTX/Met, *N* = 231, *n* (%)	p[b]
Overall	195 (82.6)	189 (81.8)	
Nausea	91 (38.6)	64 (27.7)	0.014
Vomiting	55 (23.3)	41 (17.7)	
Diarrhoea	42 (17.8)	40 (17.3)	
Abscess	23 (9.7)	15 (6.5)	
Abdominal pain	22 (9.3)	16 (6.9)	
Leucocytosis	19 (8.1)	4 (1.7)	0.002
Local reaction to procedure	18 (7.6)	14 (6.1)	
Fever	17 (7.2)	18 (7.8)	
Infection	17 (7.2)	9 (3.9)	
Anaemia	16 (6.8)	8 (3.5)	
Hypokalaemia	16 (6.8)	21 (9.1)	
Headache	14 (5.9)	22 (9.5)	
Insomnia	23 (9.7)	24 (10.4)	
Constipation	14 (5.9)	14 (6.1)	
Thrombocythaemia	13 (5.5)	15 (6.5)	
Pruritis	13 (5.5)	12 (5.2)	
Hypoproteinaemia	11 (4.7)	4 (1.7)	
Abnormal healing	9 (3.8)	8 (3.5)	
Hyperglycaemia	9 (3.8)	8 (3.5)	
Hypertension	9 (3.8)	11 (4.8)	
Peripheral oedema	9 (3.8)	7 (3.0)	
Pharyngitis	9 (3.8)	8 (3.5)	
Ileus	8 (3.4)	16 (6.9)	
Deep venous thrombosis	8 (3.4)	1 (0.4)	0.037
Oral moniliasis	8 (3.4)	1 (0.4)	0.037
Anxiety	7 (3.0)	12 (5.2)	
Pulmonary physical finding	7 (3.0)	6 (2.6)	
Respiratory failure	6 (2.5)	10 (4.3)	
Abdominal distention	5 (2.1)	11 (4.8)	
Dyspnea	5 (2.1)	7 (3.0)	
Pleural effusions	4 (1.7)	7 (3.0)	
Rash	4 (1.7)	7 (3.0)	
Taste perversion	2 (0.8)	9 (3.9)	0.035
Generalized oedema	1 (0.4)	7 (3.0)	0.036
Atelectasis	0 (0.0)	7 (3.0)	0.007

[a]A treatment-emergent adverse event is defined as any adverse event that was present from the day of first administration of study drug until 15 days after the last administration of study drug.
[b]Adverse event is reported if incidence is ≥3.0% or p <0.05.
TGC, Tigecycline; CTX/MET, ceftriaxone plus metronidazole.

Seven subjects in the mITT population died during the study: four of 236 TGC-treated and three of 231 CTX/MET-treated subjects. There were no deaths in subjects who were randomized but received no study drug. SAEs with an outcome of death in TGC-treated subjects included aspiration pneumonia, cerebrovascular accident, gastrointestinal carcinoma, septic shock, and cardiac arrest. SAEs with an outcome of death in CTX/MET-treated subjects included congestive heart failure, coronary heart disorder, respiratory failure and retroperitoneal haemorrhage. None of the deaths were considered to be related to study drug.

Discussion

cIAIs often present with peritonitis and may involve intra-abdominal abscess [7]. They develop from a primary source in the gastrointestinal tract and are associated with significant morbidity and mortality. Intra-abdominal infections are associated with an overall mortality rate of approximately 6%, with age, the source of infection and burden of co-morbidities affecting outcome [8]. Management involves fluid resuscitation, source control and appropriate antimicrobial therapy.

Inadequate antimicrobial treatment is independently associated with outcome [9,10]. The choice of empiric antibiotic therapy is complicated in the case of bacterial resistance [11] and the increasing numbers of extended-spectrum β-lactamase-producing Gram-negative bacteria, including CTX-M-type producing *E. coli* and multidrug-resistant strains of *B. fragilis*, which may be more prevalent among high-risk, hospitalized patients [11–13]. The authors of current guidelines have not concluded that one antibacterial regimen is superior to the other but emphasize the importance of broad-spectrum agents covering resistant pathogens [7,12].

The present study evaluated the safety and efficacy of tigecycline in treating hospitalized subjects with cIAI vs. an antibiotic regimen different from that used in the tigecycline registration trials. TGC met the statistical criteria for non-inferiority to CTX/MET in the primary analysis with a clinical cure rate of 70% vs. 74% in the comparator population. The study design did not require a specific distribution of cIAI diagnosis or restrict the number of subjects with an APACHE score <10. As such, 51.6% of subjects had a diagnosis of complicated appendicitis and 78.5% of subjects had an APACHE II score <10. Although it is encouraging that TGC cure rates were similar to those obtained with CTX/MET across all cIAI diagnoses and in subjects with an APACHE II score >10, the sample size is small and additional studies are required in more severely ill populations.

At the microbiological level, efficacy comparisons confirmed the results of the primary analysis. In the ME population, the clinical cure rates for those infected with the most common pathogens (i.e. *E. coli* and *B. fragilis* group members were 69.8% vs. 66.3%, and 63.8% vs. 65.4% when treated withTGC and CTX/MET, respectively).

There were no significant differences overall between the two treatment arms with respect to SAEs or TEAEs. TGC-treated subjects were significantly more likely to have nausea, oral moniliasis, leukocytosis and deep venous thrombosis. CTX/MET subjects were significantly more likely to have generalized oedema, atelectasis and taste perversion.

The results obtained in the present study are consistent with the findings of previous phase 3 trials and confirm that TGC has good activity against the pathogens associated with cIAI and is an effective and well-tolerated monotherapy option for the treatment of adult patients with cIAI [5,6,13]. In areas where multidrug-resistant pathogens are being reported, tigecycline may offer an alternative to the combination of a cephalosporin plus metronidazole, particularly where extended-spectrum β-lactamase-producing organisms have reached high levels. Further data are needed to justify the use of empiric TGC monotherapy.

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Transparency Declarations

This study was sponsored by Wyeth which was acquired by Pfizer Inc. in October 2009.

T. Babinchak and H. Leister are employees of Wyeth Research. S. Towfigh, J. Pasternak and A. Poirier have no conflicts of interest to declare.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Subject demographics, baseline data, duration of hospitalization and time to deferevescence (modified intent-to-treat population).

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